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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	16

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/445,375	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Eirc Jon Angell	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,24,25,27-29,31-34,36-38,40-43 and 45-60* is/are pending in the application.

4a) Of the above claim(s) *40-43,45,46 and 54-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,24,25,27-29,31-34,36-38,47-53 and 57-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s) _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-21, 24, 25, 27-29, 31-34, 36-38, 40-43 and 45-60 are pending in the application.

Claims 22, 23, 26, 30, 35, 39 and 44 have been canceled as requested in paper filing received December 6, 1999.

Claims 54-56 are withdrawn from consideration because they depend on claim 30, which has been canceled.

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-21, 24, 25, 27-29, 31-34, 36-38, 40 and 47-60) in Paper No. 15, received August 23, 2001, is acknowledged. Non-elected claims 41-43, 45 and 46 have been withdrawn from consideration.

Double Patenting

2. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The

filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 58 be found allowable, claim 59 will be objected to under 37 CFR 1.75 as being a duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 58 and 59 are identical claims.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1, 2, 3, 5, 6, 7, 8, 9, 10, 13, 14, 15, 17, 18, 19, 20, 21, 27, 28, 29, 31, 32, 34, 37, 38, 40, 49, 50, 51, 52, 53, 57, 58, 59 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Stringer (WO 96/15238).

Stringer teaches recombinant T lymphocytes produced by transfecting the T lymphocytes with a vector encoding heterologous alpha and beta T cell receptor (TcR) polypeptides. The heterologous TcRs confer specificity for disease causing target cells (see abstract, and page 17,

lines 15-25, for example), including tumor cells (see page 16 line 20). TcRs recognize antigen as part of a cell surface glycoprotein complex (see page 2, lines 7-15, for example), thus the alpha and beta TcR polynucleotides encode tumor-binding proteins that interact with molecules on the surface of the tumor. Furthermore, the TcRs may be expressed as a single fusion polypeptide (see page 16 lines 12-15), and the vector may be a retroviral vector (see page 21, line 11). The T-lymphocytes may be derived from a patient, transfected with the vector, and reintroduced into the patient (see page 22 lines 7-14). The vector may be operably linked to an expression element or elements to provide expression of the TcR polypeptides at suitable levels and the elements can be of any form as long as they direct or control the expression of the genes with which they are coupled (see page 19, lines 5-12). The vector described by Stringer et al. is comprised of a polynucleotide encoding a protein that specifically interacts with a tumor cell and is capable of delivering a second nucleotide to the tumor. The alpha and beta polypeptides are useful in developing cells for targeted immunotherapy (see abstract, for example) and are therefore therapeutic. The alpha and beta chains of TcR comprise constant and variable regions which are homologous to immunoglobulin V and C regions (see page 3, line 15-17). The targeted T lymphocytes comprised of the alpha and beta TcR expression vector constitutes an in vivo gene delivery system that can deliver the vector to tumor cells including those of haematapoietic lineage.

5. Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 15, 16, 20, 24, 27, 28, 29, 31, 32, 34, 47, 49, 50, 51, 52, 53, 57, 58, 59 and 60 rejected under 35 U.S.C. 102(e) as being anticipated by Wickham et al. (US Patent number: 5,559,099, 1996).

The instant claims are drawn to a vector comprising polynucleotides that encode tumor interacting proteins and therapeutic polypeptides that may be expressed as fusion proteins and are delivered to a tumor.

Wickham et al. teaches a recombinant adenovirus comprising a chimeric penton base protein, which includes a non-penton base sequence, and a therapeutic gene, a method of gene therapy involving the use of such adenovirus (see abstract). The invention provides for a cell receptor-specific/tissue receptor-specific adenovirus (see column 4 lines 13-15, and claim 1). The chimeric protein is specific for binding to a receptor (see column 4 line 52-53, and claim 1), thus adenovirus encodes a polypeptide that recognizes and binds to a molecule on the surface of the target cell. The adenovirus additionally comprises a gene capable of being expressed in a cell to which the virus is attached or by which the virus has been internalized (see column 5, lines 34-39, and claim 1). The adenovirus may be used to treat certain diseases including cancer (see column 9, lines 37-39).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 20, 21, 24, 25, 27, 28, 29, 33, 34, 38, 49, 50, 51, 52, 53, 58, and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to vectors and methods for delivering the vectors cancerous cells wherein the vectors are comprised of a polynucleotide or polynucleotides, as well as to methods of treating or ameliorating cancer. Methods of targeting nucleic acids into an organism fall in to the broad category of gene therapy. While delivery of nucleic acids in and of itself is not considered a therapy per se, delivery shares many of the obstacles recognized for many of the actual therapy methods because successful therapy methods are for the most part, based on the ability to deliver exogenous nucleic acids to cells or tissues of interest. Thus, the rejection as a whole is appropriate for the claimed invention regardless of the embodiment (delivery vs. treatment) envisaged.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient delivery and expression of genes encoding the protein in the target cells had not been fully developed. Clinical efficacy has not been achieved in any gene therapy protocol to date. The art is plagued by unpredictability. Regarding gene delivery and gene therapy, Anderson (Nature, April 30, 1998) teaches that, "[g]ene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease." Anderson (1998) also states, "[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered", and " [t]he reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defences (sic) can be overcome, and how to manufacture efficiently the vectors that we do make" (see page 30 under Conclusion). Furthermore, Verma et al (1997)

teaches, "[t]here is still no single outcome that we can point to as a success story" (see Gene Therapy Promises, Problems and Prospects, Nature, Vol. 389, pg. 239, col. 1). Walther and Stein (2000) indicate that the majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy (see pg. 267, discussion column). Mountain (2000) teaches that, "each gene transfer system has its own combination of advantages and limitations" (See Gene Therapy: the first decade, col. 5, pg. 121).

The claims are not enabled because the specification merely discloses instructions of how to construct vectors, and prophetic examples of how the vectors may be delivered to tumors and possible animal models that may prove to be useful in evaluating the efficacy of the proposed treatment. The specification does not disclose any evidence that the vectors actually deliver the polynucleotide(s) to the tumor, as required by the claims, or that the methods are effective at treating or ameliorating cancer. Such a disclosure is required in light of the relevant art that teaches the efficacy of gene therapy is unpredictable.

Thus to overcome the teachings in the art, the specification would need to supply direct, correlative guidance as to how to effectively administer the polynucleotides of interest. Also, required is evidence that the methods are effective at treating or ameliorating cancer. Without such guidance in the specification and lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of success on the part of the skilled artisan.

In conclusion, given the nature of the invention, the level of predictability, the amount of guidance set forth in the specification, and the working examples set forth, it is concluded that

one of skill in the art would need to perform a vast amount of experimentation in order to practice the invention commensurate in scope with the claims and this amount of experimentation is in fact undue.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-21, 24, 25, 27-29, 32, 33, 34, 36, 37, 38, 40, 47, 48, 49, 50, 51, 52, 53, 58, 59 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 7, 9, 36 and 47 are indefinite because these claims recite the phrase "capable of". For instance, claim 1 recites, "the tumor interacting protein is capable of recognizing a tumor, wherein the vector is capable of delivering a second polynucleotide of interest to the tumor; claim 7 recites, "tumor binding protein capable of interacting with at least one tumor-associated cell surface molecule"; and claim 36 recites, "fusion protein is capable of being secreted." The phrase "capable of" renders the claims indefinite because it is unclear as to whether 1) the protein actually recognizes a tumor, 2) the vector actually delivers the polynucleotide, 3) the protein actually interacts with the tumor associated cell surface marker, and 4) the fusion protein is actually secreted. The claims should be amended to definitively state that the protein recognizes a tumor, the vector delivers the polynucleotide, the protein interacts with the tumor associated cell surface marker, and the fusion protein is secreted. Furthermore, it is unclear what constitutes "recognizes", "delivers" and "interacts" in claims 1, 4, 7, 9, 36 and

47: thus the metes and bounds of the claims cannot be established and the claims are therefore indefinite. Additionally, claim 47 recites the limitation "protein product of interest" in line 2. There is insufficient antecedent basis for this limitation in the claim because claim 1 does not recite a protein product of interest. All of the claims that depend on claim 1 are rejected for the same reason

Claim 6 is unclear because it is unclear how the second polynucleotide of interest **"expresses"** a protein product of interest (emphasis added). The claim should be amended to state, for example, that the second polynucleotide of interest encodes a protein product of interest.

Claim 8 recites the phrase " selectively expressed on one cell type or a restrictive number of cell types". However, it is not clear what constitutes "a restrictive number of cell types" and how "one" differs from "a restrictive number" of cell types. Therefore the metes and bounds of the claims cannot be established rendering the claim indefinite.

Claim 14 recites the limitation "product of interest" in line 2. There is insufficient antecedent basis for this limitation in the claim, because there is no prior recitation of a "product of interest" in claim 1.

Claim 15 and 16 recites "functional component"; however, the specification only defines what **preferably** constitutes a functional component (see page 12 line 4 of the specification). Therefore, the term "functional component" is not clearly defined and it is not clear what is and what is not encompassed by the term "functional component". Thus, the metes and bounds of the claims cannot be determined and the claims are indefinite. Furthermore, claim 16 recites, "the vector according to claim 6 wherein any protein... further comprises at least one additional

functional component." Claim 16 it appears to be referring to two proteins recited in claim 6 (the tumor interacting protein and the product of interest), however claim 6 appears to only disclose a protein product of interest." Claim 6 or 16 should be amended to make claim 16 more clear.

Claim 17 recites the term "signaling entity"; however, the specification does not define what constitutes a "signaling entity" therefore this claim is unclear and indefinite.

Claim 18 recites the phrase "wherein the vector comprises a retroviral vector." It is unclear how a vector can comprise a vector; therefore the claim requires amendment. For example a suggestion is "wherein the vector is a retroviral vector".

Claim 20 recites, "a method of delivering a polynucleotide of interest or a product of interest said polynucleotide of interest to a tumor, comprising..." This recitation is unclear and confusing and should be amended. For example, deleting "said polynucleotide of interest" would make the claim clearer. Additionally, the phrase "product of interest" is undefined and unclear. Assuming the product of interest is a protein encoded by the polynucleotide, it is still unclear how a vector could deliver a protein product of interest to a tumor when vectors are comprised of nucleic acids and deliver polynucleotides to cells, not protein.

Claim 24 recites, "delivering wherein the polynucleotide of interest or product of interest **are** delivered..." (emphasis added). It is unclear if both products are delivered together, or if one or the other is delivered alone. Amendment is required to make the claim clear. Furthermore, the phrase "product of interest" is undefined and unclear. However, assuming the product of interest is a protein encoded by the polynucleotide, it is still unclear how a vector could deliver a protein product of interest to a tumor when vectors are comprised of nucleic acids and deliver polynucleotides to cells, not protein.

Claim 27 is indefinite because the phrase "a gene delivery system... comprising a genetic vector encoding a tumor interacting protein and an *in vivo* gene delivery system". It is unclear if the gene delivery system is composed of: 1) vector encoding a tumor interacting protein AND 2) an in vivo gene delivery system, or if the gene delivery system is composed of A vector that encodes 1) a tumor interacting protein and 2) an in vivo gene delivery system. It is also unclear if the gene delivery system is comprised of the vector, or if the tumor that is being targeted is composed of the vector. Furthermore, the "genetic vector" can be viral or non-viral vector, but the *in vivo* gene delivery system is not defined for a viral vector. The specification discloses that **non-viral** delivery systems include but are not limited to DNA transfection methods where transfection includes a process using a non-viral vector to deliver a gene to a target mammalian cell (see page 13 of the specification starting on line 14). A list of typical transfection methods is also disclosed, including electroporation, DNA biolistics, lipid mediated transfection, compacted DNA-mediated transfection, and so forth (also see page 13 of the specification starting on line 17). If the claim states that the system includes a vector AND an in vivo gene delivery system, it is unclear what the in vivo gene delivery system would be when the vector is a viral vector. All of the claims that depend on claim 27 are rejected for the same reason.

Claim 28 recites, "a method of treating cancer comprising administering the gene delivery system according to claim 27 to the site of a tumor." This is unclear and confusing because it may be construed that claim 28 is referring to "administrating" as described in claim 27. However, claim 27 refers only to a gene delivery system, not to administration of the system. Alternatively, the claim may be read as administrating the gene delivery system of claim

27. The claim can be interpreted in more than one way; therefore it is ambiguous and needs to be amended to eliminate the ambiguity.

Claim 29 recites, "the method of claim 28 wherein the tumor is of haematopoietic cell lineage." It is unclear what the site of a tumor would be when the tumor is of haematopoietic lineage. The phrase "site of the tumor" implies a solid mass of cells, however cancerous haematopoietic cells do not form solid tumors and it is therefore unclear what the site of a haematopoietic tumor would be.

Claim 32 recites the phrase, " effector domain". This phrase is unclear because it is unclear what constitutes an "effector domain".

Claim 33 is unclear because the phrase "one or more tumor-interacting protein genes" is confusing. The claim requires amendment. An acceptable example is, "one or more genes encoding tumor interacting proteins". All of the claims that depend on claim 33 are rejected for that same reason

Claim 34 is unclear because the phrase "a combination of a cytokine or a cytokine – encoding gene and one or more tumor-interacting protein encoding genes" is confusing. It is unclear how a protein can encode a gene. The claim requires amendment amended. An acceptable example is, " a combination of a cytokine or a gene encoding a cytokine and one or more genes encoding tumor-interacting proteins". Furthermore, the phrase, "to the site of a

tumor" is vague, because the boundary of "the site of a tumor" is undefined. It is unclear exactly what would be and what would not be considered the site of a tumor. For instance, it is unclear if simple administration of the gene to an organism that has a tumor would be considered delivery to the site of the tumor.

Claim 38 is indefinite because the recitation "in close association with a second cell" is vague. It is unclear what would constitute "in close association" and there is no definition of "in close association" in the specification. Without a clear definition of the phrase "in close association", the metes and bounds of the claim cannot be determined. For instance it is unclear if merely injecting the first cell into the blood stream would constitute "in close association" or if the cells need to be touching to be considered "in close association".

Claim 40 recites, "A process for preparing a tumor-binding protein comprising expressing a polynucleotide encoding a tumor-binding protein in a vector according to claim 1." This is unclear and confusing because it may be construed that claim 40 is referring to "a process" as described in claim 1. However, claim 1 only refers only to a vector, not to a process for making protein. Alternatively, the claim may be read as a process for making a protein using the vector of claim 1. The claim can be interpreted in more than one way; therefore, it is ambiguous and needs to be amended to eliminate the ambiguity.

Claims 49 and 50 recite, "the method... wherein the vector is used to deliver the polynucleotide of interest and/or product of interest *in vivo* to the tumor." These claims are

indefinite because it is unclear how the vector can deliver can deliver a polynucleotide of interest and product of interest. The "product of interest" is undefined and therefore unclear. However, assuming the product of interest is a protein encoded by the polynucleotide, it is still unclear how a vector could deliver a protein product of interest to a tumor when vectors are comprised of nucleic acids and deliver polynucleotides to cells, not protein.

Claim 51 recites the "wherein the tumor-interacting protein is a TBP." The abbreviation "TBP" is unclear because it is not defined in the claim. TBP could be construed to mean TATA Binding Protein or Tumor Binding Protein. It is suggested that the claim be amended to eliminate the unclear abbreviation.

Claim 52 recites, "the method of claim 28 wherein the gene delivery system is administered systemically." The phrase "administered systemically" renders this claim indefinite because it is unclear what is encompassed by this limitation. For instance, it is unclear if oral administration, administration to the skin (such as a topical lotion), administration by injection and administration by inhalation (such as an aerosol) would constitute systemic administration. Without a clear definition of the phrase "administered systemically" the metes and bounds or this claim cannot be determined.

Claim 60 recites the limitation "protein product of interest" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 40 does not recite a "protein product of interest", thus claim 60 is indefinite.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Clark can be reached on (703) 305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
October 22, 2001

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/